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(54) Title: TABLET FOR USE IN THE TREATMENT OF PROGESTERONE DEFICIENCY

(57) Abstract

A tablet comprises micronized progesterone blended with carnuba wax and safflower oil that produces sustained serum level increases of progesterone. The concentration of the wax is between 20 % and 150 % by weight of that of the progesterone. The particle size of the progesterone is largely below 10 microns. By thoroughly blending micronized natural progesterone with a wax having a melting point above body temperature, such as carnuba wax, degradation of the progesterone by the liver is sufficiently limited so as to achieve good serum level increases in progesterone on a sustained and substantially predictable basis. The inclusion of a limited quantity of safflower oil has also been found to be beneficial in this regard.

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TABLET FOR USE IN THE TREATMENT OF PROGESTERONE DEFICIENCY

TECHNICAL FIELD

This invention relates generally to the administration of progesterone in the treatment of progesterone deficiency in the human female, and particularly to tabletized progesterone compositions.

BACKGROUND OF THE INVENTION

Progesterone is a naturally occurring steroid which is biosynthesized in the ovaries and the adrenal cortices in nonpregnant women. Progesterone is medically administered in the treatment of progesterone deficiency as well as in the treatment of other disorders such as pregnancy complications and menstrual abnormalities. Even though it has been synthesized commercially since 1934, its clinical usefulness has been limited because of its extensive degradation by the liver following ingestion and because of its short shelf life.

Orally administered, synthetic progestational agents known as progestins, which do not degrade rapidly, have been used for treatment of some disorders. They however produce undesirable side effects. Thus efforts have continued to devise a manner to administer natural progesterone. Since intramuscular injection of

progesterone is not therapeutically practical, and since vaginal and rectal administration is inconvenient and aesthetically displeasing, attempts have continued to develop a natural progesterone composition that can be administered orally.

Heretofore, two general approaches have been taken in attempts to circumvent the effect that the liver has on orally administered progesterone. One involves bypassing the liver by giving oily preparations of progesterone to encourage its absorption through the lymphatic system. Laboratoires Besins Iscovesco of Paris, France has followed this approach by developing a soft gelatin capsule marketed in Europe under the name Utrogestan. It has progesterone combined with a vegetable oil in gelatin. Its effectiveness however has been limited since serum levels of progesterone following its administration have been found to be erratic, non predictable and not characterized by sustained release. Moreover, its production is messy and inefficient by being encapsulated in gelatin.

The other approach is to micronize the progesterone by placing it in powdered form in an environment that creates breakage of the particles to very small sizes, mostly under 10 microns. In micronized form it is absorbed so rapidly that massive dosages saturate the metabolic capacity of the liver to a point that a significant amount can go through the liver without breakdown. Massive dosages for any significant period, however, would be both clinically harmful and not economically feasible.

Accordingly, it is seen that a need remains for a pharmaceutical product by which natural progesterone may be orally administered with effective absorption rates, improved shelf life, with sustained release properties and in moderate dosages.

SUMMARY OF THE INVENTION

It has now been discovered that a tabletized mixture of micronized progesterone and a wax is effective in elevating serum levels of progesterone. The concentration of the wax is between 20% and 150% by weight of that of the progesterone. The particle size of the progesterone is largely below 10 microns. By thoroughly blending micronized natural progesterone with a wax having a melting point above body temperature, such as carnauba wax, degradation of the progesterone by the liver is sufficiently limited so as to achieve good serum level increases in progesterone on a sustained and substantially predictable basis. The inclusion of a limited quantity of safflower oil has also been found to be beneficial in this regard.

EXAMPLE I

micronized progesterone	1000 grams
Brazilian carnauba wax	1000 grams
Avicel 102	1000 grams
microsilica gel	15 grams
stearic acid	30 grams
AC DI SOL	30 grams
magnesium stearate	15 grams

The preparation is made by placing the progesterone in micronized, powdered form having particle sizes less than about 10 microns into a blender with the powdered Brazilian carnauba wax and blending the mixture for 15 minutes. The Avicel 102, AC DI SOL, the microsilica gel and stearic acid are premixed to a uniform blend and then thoroughly blended with the progesterone and wax mixture for 10 minutes. Following this the magnesium stearate is added to the mixture and blended for another 5 minutes. The blend is then conventionally compressed to form

tablets that are stored under refrigeration at 40°F or less.

Clinical studies have found that the oral ingestion during the midluteal phase of the menstrual cycle of tablets having 100 milligrams of progesterone in the morning and having 200 milligrams of progesterone at bedtime, of the Example I composition, increases the serum concentration of progesterone for sustained periods of time sufficient to evoke progestinal responses in the responsive end organs. Clinical tests have shown the following serum levels to be achieved:

TABLE I

	Dosage in milligrams	
	100	200
Peak Time (hours)	4-5	4-5
Peak concentration (ng/ml)	3.9	10.2
Range at peak (ng/ml)	1.8-5.9	4.7-18.5
Surface area under curve*	43	100
No. participants	9	5

*Curve being a plot of serum progesterone in ng/ml against time in hours.

Though the physiological mechanism at work here is still not fully understood, apparently the presence of the wax finely blended with progesterone in micronized form limits the effectiveness of the liver in degrading the progesterone during liver transit. Thus, micronized progesterone enters into the bowel in sufficient quantity to be available for absorption at effective rates with the administration of only the three tablets per day of 100 mg progesterone each. Not only does it enter the

bowel in sufficient quantity but it also is present there for release from the wax at good sustained release rates.

The Avicel 102 cellulose filler is added to provide bulk. It should be present in a concentration of 20% to 50% of total weight. The AC DI SOL, a specialized cellulose filler, is provided at 1/2% to 1% of total weight as a disintegrant. The stearic acid and magnesium stearate serve as lubricants to prevent adherence of the composition to the tabletizing apparatus. The stearic acid and magnesium stearate are each provided at 1% to 2% of total tablet weight. The microsilica gel acts as a desiccant and flowing agent and should be present from 0.5% to 2% of total weight. The wax must have a melting point above body temperature and should be at a concentration of 20% to 150% by weight of the progesterone. Concentrations of less than 20% suffer from adverse losses of absorption and of sustain release properties. Concentrations above 150% restrict absorption of the progesterone from the intestinal track.

EXAMPLE II

micronized progesterone	200 mg
Brazilian carnauba wax	100 mg
silica-based excipient*	400 mg
safflower oil	50 mg
silica powder	2%
stearic acid	1%
magnesium stearate	1%

*Micosolle, available from Biomicotek, Inc. of Torrance, California

Post-menopausal women were orally administered 200 mg of the preparation in tablet form while fasting. Blood samples were obtained hourly for 6 hours, then at 8 hours and 24 hours. Serum progesterone was measured by

radioimmunoassay and bioavailability was assessed by measuring the area under the curve of serum progesterone levels for 8 hours. For comparison, post-menopausal women were orally administered the same preparation with zero safflower oil content and with 200 mg safflower oil. The results are shown in Table II.

TABLE II

Safflower oil/ progesterone ratio	Mean surface area under curve to 8 hours*	Number of Subjects
0	100	5
0.25	249	12
1.0	187	8

*Curve being a plot of serum progesterone in ng/ml against time in hours.

It thus is seen that the bioavailability of orally ingested micronized progesterone was increased significantly with the addition of safflower oil in limited quantities.

The preparations with safflower oil are prepared by mixing micronized progesterone with the safflower oil and then adding the carnauba wax. The excipient Micosolle is added to provide sufficient hardness to the table and for flowability of the powder during compression. The magnesium stearate, stearic acid and silica are then added, thoroughly mixed and the preparation conventionally compressed.

CLAIMS

1. A pharmaceutical composition suitable for orally administering progesterone comprising a tabletized mixture of progesterone in powdered form and a wax in powdered form having a melting point above body temperature.

2. The composition of claim 1 wherein said progesterone has particle sizes generally less than 10 microns.

3. The composition of claim 1 wherein said wax is present at a concentration of between 20% and 150% by weight that of said progesterone.

4. The composition of claim 1 wherein said wax is carnauba wax

5. The composition of claim 1 further comprising a cellulose filler in an amount of between 20% and 50% of total composition weight.

6. The composition of claim 1 further comprising 1% to 2% of total weight of magnesium stearate as a lubricating agent.

7. The composition of claim 1 further comprising 1% to 2% of total weight of microsilica gel as a flow agent.

8. The composition of claim 1 further comprising 1% to 2% of total composition weight of stearic acid as a lubricant.

9. The composition of claim 1 further comprising safflower oil.

10. The composition of claim 9 wherein safflower oil is present at a concentration not exceeding that of the progesterone concentration.

11. A method of making a tablet for oral ingestion to elevate blood level contents of progesterone wherein the method comprises the steps of (a) mixing progesterone in powder form with a wax in powdered form; (b) blending the mixture of progesterone and wax; (c) adding a filler in powdered form to the mixture; (d) blending the mixture of progesterone, wax and filler, and (3) compressing the blended mixture.

12. The method of claim 11 wherein step (a) progesterone in powder form is mixed with carnauba wax in powder form.

13. The method of claim 11 wherein step (a) progesterone in powder form of a particle size less than 10 microns is mixed with wax in powder form.

14. The method of claim 11 wherein step (a) the powdered wax is mixed with powder progesterone in a concentration of between 20% and 150% by weight of the progesterone.

15. The method of claim 11 wherein step (c) a cellulose filler is added to the mixture in an amount between 20% and 50% by weight of the total weight of the composition.

16. The method of treating progesterone deficiency in the human female which comprises the steps of orally administering a tablet comprised of a mixture of powdered progesterone and powdered wax with the concentration of wax in the tablet being sufficient to achieve rendered sustained release of progesterone after passage through the liver.

17. The treatment method of claim 16 wherein the tablet is orally administered during the midluteal phase of the menstrual cycle.

18. The treatment method of claim 16 wherein the orally administered tablet also comprises safflower oil.

19. The method of making a tablet for oral ingestion to elevate blood level contents of progesterone wherein the method comprises the steps of:

(a) mixing progesterone in powder form with safflower oil;

(b) adding carnauba wax and blending the mixture of progesterone, safflower oil and wax;

(c) adding an excipient; and

(d) blending and compressing the blended mixture in tablet form.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US88/03406

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

INT. CL[4] A61K 31/56; A61K 47/00
U.S. CL. 424/465, 468, 469

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
U.S.	424/465, 468, 469

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
Y	US,A, 3,535,419 (SIEGRIST ET AL) 20 October 1970, See column 4, lines 12-16	1-19
Y	US,A, 3,459,850 (RIVA) 05 August 1969, See column 3, lines 55-62	1-19
Y	US,A, 3,402,240 (HOHOKUS ET AL) 17 September 1968, See column 1, lines 31-48	1-19
Y	US,A 3,193,457 (KINEL) 06 July 1965, See column 2, line 31-55	1-19
Y	US,A, 2,895,881 (HAMADA) 21 July 1959, See columns 2 and 3	1-19
Y	US,A, 2,880,135 (EPPSTEIN) 31 March 1959, See column 2, lines 1-37	1-19

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search

24 January 1989

Date of Mailing of this International Search Report

07 MAR 1989

International Searching Authority

ISA/US

Signature of Authorized Officer

Karl Group

Form PCT/ISA/210 (second sheet) (Rev.11-87)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
A	US,A, 4,439,432 (PEAT) 27 March 1984	1-19
A	US,A, 4,209,513 (TORODE ET AL) 24 June 1980	1-19
A	US,A, 4,159,346 (OMURA ET AL) 26 June 1979	1-19
A	US,A, 3,920,630 (WECHTER ET AL) 18 November 1975	1-19